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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/788,800	01/22/97	BEDNAR M	P0987R1

HM21/0528

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EXAMINER
GAMBEL, P

ART UNIT	PAPER NUMBER
1642	#10

DATE MAILED: 05/28/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)
*U.S. GPO: 1997-422-198/60031

1- File Copy

Office Action Summary	Application No. 08/788,800	Applicant(s) Bednar et al.
	Examiner GAMBEL	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Mar 5, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-12 and 15-17* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12 and 15-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1642, Technology Center 1600

2. Applicant's amendment, filed 3/5/98 (Paper No. 8), is acknowledged.
Claims 13-14 have been canceled.
Claims 1, 10, 11, 15 and 17 have been amended.
Claims 1-12 and 15-17 are pending and being acted upon presently.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 3/5/98 (Paper No. 8).
The rejections of record can be found in the previous Office Action (Paper No. 5).

4. Applicant's amendment, filed 3/5/98 (Paper No. 8), indicates that a petition was filed to convert priority application USSN 08/589,982 to a provisional application. Applicant cannot update the related application information as set forth in the previous Office Action (Paper No. 5) and reiterated herein, since the PTO has not assigned a provisional application serial number yet.

It is noted that USSN 08/589,982 has been abandoned and has NOT been converted to a provisional application at this time. It appears that applicant's petition, filed 1/14/97, has not been matched to USSN 08/589,952. Applicant is invited to consider refiling the petition with appropriate postcard receipts. For applicant's convenience, it is noted that the examiner of instant USSN 08/788,800 has retrieved priority USSN 08/589,952 from its previous location.

Furthermore, applicant has not satisfied the formal requirements of setting forth priority to USSN 08/589,982 either in the oath/declaration or on the first line of the specification. Therefore, applicant does not receive priority to 1/13/96 until such requirements are fulfilled.

In addition, it is noted that the instant USSN 08/788,800 would be considered a CIP of priority USSN 08/589,982, since the instant application discloses and claims sequences not disclosed in the priority application. However, it appears that the sequences disclosed in the instant application are inherent properties of the humanized antibody disclosed and claimed in the priority application, therefore the priority date would be considered 1/13/96, when the formal requirements of priority are satisfied in the instant application.

The following is a reiteration of priority issues, as set forth in the previous Office Action (Paper No. 5).

If applicant desires priority under 35 U.S.C. 119(e) or 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant's claim to a "Serial No. To Be Assigned", filed 1/23/96, in the Oath and on the first line of the Specification is acknowledged. However, applicant has not provided the serial number of the application relied upon for priority. Therefore, at this time, the filing date of the instant application is considered to be the filing date of the instant USSN 08/788,800, that is, 1/22/97. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

5. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 5.

Applicant seeks to defer formal drawings until allowance..

6. Upon reconsideration of applicant's amendment, filed 3/5/98 (Paper No. 8), indicating and reciting the entire amino acid sequence of the humanized H52 antibody; the previous requirements under 35 USC 112, first paragraph, for the deposit of the hybridoma which produces the H52 antibody has been withdrawn.

7. The cancellation of claim 13 has obviated the previous rejection under 35 U.S.C. 112, first paragraph, because with respect to salvage receptor binding epitopes.

8. Claims 1-12 and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for anti-CD18 antibodies which bind to the CD18 epitope to which either MHM23 or H52 binds or which bind the CD18 antigen with affinity of 4nm or less or which dissociate the CD11b and CD18 complex, does not reasonably provide enablement for other CD18 specificities. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use other CD18 specificities commensurate in scope with the claimed methods. There is insufficient direction and guidance to enable one of ordinary skill in the art to make and use any anti-CD18 antibodies to treat focal ischemic stroke wherein cerebral blood flow is increase or infarct size is reduced upon administration of anti-CD18 antibody in the absence of removal of the arterial obstruction in a manner reasonably correlated with the scope of the claims broadly including any number of anti-CD18 antibodies. Given applicant's arguments, filed 3/5/98 (Paper No. 8), which distinguishes the ability of anti-CD18 antibodies of the prior art to meet the claimed limitation of "in the absence of removal of the arterial obstruction". There is insufficient objective evidence to support any anti-CD18 antibodies to meet the requirements of the claimed methods. The scope of the claims must bear a reasonable correlation with the scope of enablement. Applicant has not enabled the breadth of anti-CD18 antibody specificities broadly encompassed by the claimed methods.

It is noted if applicant recites MHM23, then the following is noted.

It is apparent that the MHM23 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

As pointed out above in section , applicant has satisfied the enablement requirements under 35 USC 112, first paragraph, with respect to the H52 specificity.

9. Upon reconsideration of applicant's amendment, filed 3/5/98 (Paper No. 8); the previous rejections under 35 U.S.C. § 112, second paragraph, have been obviated.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (f) he did not himself invent the subject matter sought to be patented.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1-12 and 15-17 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter. Priority USSN 08/589,982 discloses and claims the same instant methods except that the instant application also discloses and claims the inherent amino acid sequence of the humanized H52 antibody. However, the instant application also names Cordell Gross as an inventor of the same subject matter. Since the amino acid sequence is an inherent property of the same humanized H52 antibody disclosed and claimed in the priority application and since determining said amino acid sequence is not considered an inventive contribution; it is incumbent on applicants to provide a satisfactory showing which would lead to a reasonable conclusion that instant applicants are the inventors of the claimed invention.

13. Upon reconsideration of applicant's arguments, filed 3/5/98 (Paper No. 8); the previous rejection of claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mori et al. (Stroke, 1992) has been withdrawn.

Although it appears that the IB4 antibody meets the requirements of achieving the claimed methods, as evidenced by Bednar et al. (Neurol. Res., 1996) and applicant's arguments that Bednar et al. Is not prior art (versus arguing that it is not enabling); the conditions of Mori et al. do not meet the claimed limitation of "in the absence of removal of arterial obstruction" under 102.

14. Upon reconsideration of applicant's arguments, filed 3/5/98 (Paper No. 8); the previous rejection of claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Clark et al. (Stroke, 1991).

15. Upon reconsideration of applicant's amended claims to recite "human"; the previous rejection as it would apply to the instant claims under 35 U.S.C. § 102(a) as being anticipated by Bednar et al. (Neurol. Res., 1996).

However, the following is noted. Applicant's arguments, filed 3/5/98 (Paper No. 8), have been fully considered but are not found convincing in that applicant has not fulfilled the formal requirements to receive priority to USSN 08/589,982, as set forth in the previous Office Action (Paper No. 5) and above in section 4. Therefore, Bednar et al. remains as prior art to the instant application.

16. The cancellation of claim 13 has obviated the previous rejection under 35 U.S.C. § 103.

17. Upon reconsideration of applicant's arguments, filed 3/5/98 (Paper No. 8), and in the interest of compact prosecution, a New Grounds of Rejection employing additional references is set forth herein. ,

18. Claims 1-12 and 15-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Bednar et al. (Neurol. Res., 1996) OR Bednar et al. (Stroke, 1992; 1449, #26) OR Lindsberg et al. (J. Neurosurg, 1995) in view of Kim et al. (J. Neurological Sciences, 1995) OR Bednar et al. (Stroke, 1991; 1449, #28) Lee et al. Surgery, 1995) and in further view of known anti-inflammatory anti-CD18 specificities and art known methods at the time the invention was made to employ antibody fragments and humanized antibodies as taught by Hildreth et al. (Mol. Immunol., 1989) OR Hildreth (WO 9015076) Lee et al., (Surgery, 1995) OR Jardieu et al. (U.S. Patent No. 5,622,700).

Mori et al. teach inhibiting focal cerebral ischemia in baboons with the anti-CD18 antibody IB4 (see entire document).

Bednar et al. (Neurol. Res., 1996) teach reducing intracranial pressure following thromboembolic stroke in the rabbit with the anti-CD18 antibody IB4 (see entire document).

Bednar et al. (Stroke, 1992) teach reducing intracranial pressure following thromboembolic stroke in the rabbit with the anti-CD18 antibody IB4 (see Abstract).

Lindsberg et al. teach the ability of the anti-CD18 antibody given after the onset of reperfusion to treat a spinal-cord ischemia-reperfusion injury in rabbits (see entire document).

Mori et al., Clark et al., Bednar et al., Lindsberg et al. differ from the instant methods by not employing antibody fragments or humanized antibodies or treating human patients, however such antibody modifications were standard procedures in increasing therapeutic efficacy and in treating human patients at the time the invention was made.

Mori et al., Clark et al., Bednar et al., Lindsberg et al. differ from the instant methods by not teaching the particular claimed time frames of 45 minutes to 5 hours and 15 minutes to about 20 hours, however the references do teach treating within these time frames. In addition, such time frames as well as providing bolus/continuous infusion would have obvious to the ordinary artisan at the time the invention was made in providing sufficient anti-CD18 antibody depending on the need of the patient.

Kim et al. provide evidence that CD11a and CD18 are unregulated in patient with ischemic stroke and transient ischemic attacks and that such adhesion molecules are involved in tissue injury in various cerebral vascular disorders including ischemic stroke (see entire document).

Bednar et al. (Stroke 1991) teaches the art known role of neutrophils in the focal ischemic stroke encompassed by the claimed methods, including that neutropenia, including that induced by antibody treatment

Mori et al., Clark et al., Bednar et al., Lindsberg et al., differ from the instant claims by not disclosing the H52 specificity (as disclosed and claimed) or MHM23 specificity (as disclosed).

Both Hildreth et al. references teach the H52 specificity . Further, Hildreth (WO 90/15076) teaches the use of recombinant antibodies, antibody fragments as well as antibodies binding the same epitope to inhibit immune responses and adhesion mediated by CD18 in various therapeutic modalities. Although the references are silent about the exact sequences of the H52 antibody, the recombinant techniques and computer analyses of CDR grafting known and well-practiced at the time the invention was made would have resulted in the same or very nearly the same structural and functional characteristics of the instant humanized H52 antibody and fragments thereof, since both the references and instant invention use the same techniques, the same antibody specificities and the same goals. There appears no evidence that the instant humanized H52 antibody would differ in an unexpected or distinct manner from that available to the ordinary artisan at the time the invention was made.

Lee et al. teach the use of the MHM23 antibody specificity to inhibit ischemia-reperfusion injury in vivo (see Abstract).

In addition, Jardieu et al. teach the use of anti-CD18 antibodies such as MHM23 and H52 to inhibit LFA-1 mediated disorders, including the treatment of CNS inflammatory disorders (see Description of the Preferred Embodiments, particularly columns 7-8) as well as various recombinant antibodies and antibody fragments (see Modes for Carrying Out the Invention, particularly columns 10-12).

Therefore, the ordinary artisan was motivated with an expectation of success to inhibit immune response and leukocyte adhesion associated with a number of inflammatory conditions, including ischemic conditions with a number of anti-CD18 specificities, including the IB4, MHM23 and H52 anti-CD18 specificities.

Claims 15-17, drawn to articles or manufacture and kits would have been obvious at the time invention was made in providing anti-CD18 antibodies in a form including the instructions for its use intended for the treatment of ischemic stroke, as taught by the references above. It was well known convention in the art to place components in a kit for convenience and economy.

One of ordinary skill in the art at the time the invention was made would have been motivated to select anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Applicant's arguments, filed 3/5/98 (Paper No. 8), have been fully considered but are not found convincing for the reasons above. Applicant's arguments focus on the prior art teachings of models wherein the arterial obstruction is not removed. However, Bednar et al. appears to teach said models. Furthermore, it is clear the prior art discuss and address the use of anti-CD18 antibodies, including the analogy to the positive effects of neutropenia on stroke, including focal ischemic stroke, as a therapeutic modality. Applicant is invited to consider the Introductions and Discussions of the prior art and not just the experimental conditions of the models employed. Although certain references may rely upon reversible models or models where the arterial obstruction is not removed; the references do provide motivation and expectation of success in treating such focal ischemic conditions associated with stroke and are not limited to the conditions of the experimental models alone. Also, it is noted that applicant appears to argue that the IB4 anti-CD18 specificity, as taught by Mori et al. does not meet the claimed limitations. However, it appears that the instant applicant relies upon the use of the IB4 anti-CD18 antibody to achieve the claimed therapeutic endpoints. See Bednar et al. (Neurol. Res., 1996) and Bednar et al. (Stroke, 1992). In addition, the combination of the prior art clearly is directed to treating ischemic conditions, including conditions of focal ischemic stroke encompassed by the claimed methods, with anti-CD18 antibodies to inhibit neutrophil activity and function in order to achieve a beneficial effect in response to ischemia in vivo and to reduce brain injury.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Technology Center 1600
May 26, 1998